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Trabajo Original

Epidemiología y dietética

Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease

Los niveles de yodo están asociados con estrés oxidativo y estado antioxidante en mujeres embarazadas con enfermedad hipertensiva

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Abstract

Background: The antioxidant function of iodine and iodine deficiency as a risk factor of preeclampsia have been previously reported.

Aim: To analyze the association between iodine deficiency, oxidative stress and antioxidant status with hypertensive disease of pregnancy (HPD).

Method: Fifty-seven pregnant women were recruited in the last trimester of pregnancy; 20 were diagnosed with hypertensive disease (HPD) of pregnancy and 37 were normotensive pregnant women. Urinary iodine concentration (UIC), TSH, free T4 (fT4), total antioxidant status (FRP), superoxide dismutase (SOD), catalase (CAT), and oxidative stress (TBARS) were evaluated by colorimetric methods.

Results: UIC median for all pregnant women was 151.9 µg/l. The UIC for pregnant women with HPD was 50-149 µg/l, compared to 150-249 µg/l in normotensive women. No significant differences in levels of TSH and fT4 in normotensive pregnant compared with HPD women were found. Pregnant women with HPD had significant high levels of TBARS, and significant low levels of FRP, SOD, CAT and UIC compared to normotensive pregnant. In addition, pregnant women with optimal levels of UIC had a higher SOD activity ($r = 0.354$, $p = 0.011$), while iodine deficiency was associated with HPD ($r = -0,281$, $p = 0.039$). Similarly, pregnant women with HPD had a significant negative association with SOD activity ($r = -0.702$, $p = 0.005$), CAT ($r = -0.409$, $p = 0.002$), and FRP ($r = -0.624$, $p = 0.003$), and a positive association with TBARS ($r = 0.744$, $p = 0.001$).

Conclusion: Iodine contributes to redox balance during pregnancy; its deficiency is associated with HPD. This study shows the importance of iodine during pregnancy.

Key words:

Iodine deficiency.
Pregnancy-induced hypertension.
Oxidative stress.
Antioxidant status.

Resumen

Antecedentes: previamente se han reportado la función antioxidante del yodo y su deficiencia como un factor de riesgo de preeclampsia.

Objetivo: analizar la asociación entre la deficiencia de yodo, el estrés oxidativo y el estado antioxidante con la enfermedad hipertensiva del embarazo (HPD).

Métodos: cincuenta y siete mujeres embarazadas se reclutaron en el último trimestre del embarazo, 20 diagnosticadas de enfermedad hipertensiva del embarazo y 37 gestantes normotensas. La concentración urinaria de yodo (UIC), TSH, T4 libre (hT4), estado antioxidante total (FRP), superóxido dismutasa (SOD), catalasa (CAT), y estrés oxidativo (TBARS) se evaluaron por métodos colorimétricos.

Resultados: la mediana de UIC para todas las mujeres embarazadas fue de 151,9 µg/l. La UIC para las mujeres embarazadas con HPD fue de entre 50 y 149 µg/l, comparada con 150-249 µg/l de las gestantes normotensas. No se encontraron diferencias significativas entre los niveles de TSH y fT4 en embarazadas normotensas y en mujeres con HPD. Las mujeres embarazadas con HPD tuvieron niveles altos de TBARS y niveles bajos de FRP, SOD, CAT y UIC comparadas con las gestantes normotensas. Además, las mujeres gestantes con niveles óptimos de UIC tuvieron la actividad SOD más alta ($r = 0,354$, $p = 0,011$), mientras que la deficiencia de yodo se asoció con HPD ($r = -0,281$, $p = 0,039$). De manera similar, las gestantes con HPD tuvieron una asociación negativa con la actividad de SOD ($r = -0,702$, $p = 0,005$), CAT ($r = -0,409$, $p = 0,002$) y FRP ($r = -0,624$, $p = 0,003$), y una asociación positiva con TBARS ($r = 0,744$, $p = 0,001$).

Conclusión: el yodo coadyuva en el balance redox durante la gestación; su deficiencia está asociada con HPD. Este estudio muestra la importancia del yodo durante la gestación.

Palabras clave:

Deficiencia de yodo.
Hipertensión inducida por el embarazo.
Estrés oxidativo.
Estado antioxidante.

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INTRODUCTION

Hypertensive disorders of pregnancy are a major cause of maternal morbidity and mortality worldwide; within this group of diseases preeclampsia is very interesting because it causes about 50,000 deaths per year worldwide (1). In Mexico, hypertensive disorders of pregnancy represent about 34% of all maternal deaths, so it is considered as one of the main causes of death (2). Although there have been great advances in medicine, the frequency of this disease has not been successfully modified significantly (3). Currently, the etiology of this disease remains unknown, therefore, in order to explain its origin various theories have been raised, and within each of them the genetic origin, immune factor, endothelial dysfunction, increased oxidative stress, micronutrients deficiency, among others, can be mentioned (3-8). During pregnancy, there is a normal increase in the production of reactive oxygen species (ROS); likewise, the antioxidant capacity is increased. However, in women with hypertensive disorders an imbalance that causes increased oxidative stress has been found (9,10). It has been suggested that lipid peroxides, from altered oxidative stress, are likely promoters of maternal vascular malfunction, vasoconstriction and imbalance between thromboxane and prostacyclin, inducing endothelial cell dysfunction (8,11). Deficiency of several trace element is reported in pregnant women with preeclampsia (12). One of the most important micronutrients during pregnancy is iodine, which must be consumed through daily intake (250-300 µg/l). One of its main functions is the synthesis of thyroid hormones involved in the proper development of the fetus as well as in the regulation of various metabolic processes in adulthood. During gestation, iodine deficiency is a risk factor of preeclampsia (13-17). Iodine *per se* has several functions: bactericidal, apoptosis inducer, antioxidant, and it has been recently involved in migration, invasion and trophoblast differentiation (18-22). Regarding the role of iodine as an antioxidant, it has been proposed that it can act directly as an electron donor and compete for binding sites with free radicals (23). While in an indirect way iodine can be iodinated fatty acids derived from arachidonic acid and join a superfamily of known nuclear receptors as receptors activators peroxisomal proliferation (PPAR), which have the function of acting as transcription factors that regulate antioxidant genes activation (24-26). Iodine deficiency may be involved in the alteration of the antioxidant balance, and thus increase levels of oxidative stress, causing the development of complications during pregnancy and hypertensive disorders (5). This study aimed to establish the association between iodine levels in urine, antioxidant status and oxidative stress and women diagnosed with hypertensive disorder of pregnancy.

MATERIALS AND METHODS

PATIENTS

A case-control study in pregnant women from Xalapa, Veracruz (Mexico), who received antenatal care in the Hospital Regional Luis F. Nachón was carried out. The hospital Ethics Committee and the Bioethical Committee of the health institute of the University of Veracruz approved the study, which complies with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards. In this study, we incorporated 57 pregnant women in the third trimester between 18 and 35 years old, 20 pregnant women with hypertensive pregnant disease (HPD) as cases, and 37 normotensive pregnant as controls. Each pregnant woman signed an informed consent letter and questionnaires in order to known their sociodemographic and clinical characteristics, and food consumers were applied. The subjects with diabetes mellitus, severe anemia, and thyroid disease were excluded from this study. The blood collection and urinary sampling were carried out from January 2015 to April 2015 in the Gynecology and Obstetrics area of the Hospital Luis F. Nachón (Xalapa, Veracruz). Five milliliters of fasting venous blood were collected in BD Vacutainer® and preserved using packs of ice blocks; later, they were transported to the laboratory for the assessment of TBARS level, an indicator of oxidative stress. SOD, catalase, and total antioxidant status (TAS) were measured as indicators of antioxidant status as previously reported (5). The blood samples were centrifuged at 5,000 rpm for five minutes to separate plasma. The layers of white blood cells above the packed erythrocytes were discarded. Erythrocyte pellet was washed three times with 0.15 HCL, diluted in 33% of phosphate buffer saline (mM; NaCl, 136.9; KCl, 2.68; KH_2PO_4, 1.47; $Na_2 HPO_4$, 6.62; and pH 7.4), and kept at 4 °C until use. Similarly, the urine samples were collected and 10 ml were preserved in frozen-capped plastic tubes and 20% of formalin (two drops) were added in order to minimize iodine volatilization; then, they were frozen and analyzed. All blood samples were preserved in the refrigerator and the prooxidants and antioxidant parameters were estimated using a spectrophotometer within 48 hours of collection of the blood samples.

URINARY IODINE CONCENTRATION, TSH AND FREE T4 DETERMINATIONS

Urinary iodine concentration (UIC) was measured using a fast colorimetric method, appropriate for population studies (5,15). Briefly, 0.2 ml of serum or iodine calibrator (50-300 µg/l) and 1.0 ml of ammonium persulfate solution were heated for one hour at 100 °C. After adding arsenious acid solution (10 g of As_2C_3, 50 g of NaCl, 400 ml of 2.5 mol/l H_2SO_4) to each tube, it was mixed in a vortex mixer. Then, fresh ferroine-arsenic acid solution (10.8 mol/l H_2SO_4, arsenious acid, 200 g/l sodium chloride, and 2 ml ferroine) was added. Finally, ceric ammonium sulfate solution was added with the multipipetter, and the content of each glass tube (150 µl) was then transferred to a sterile polystyrene microtiter plate. Iodine was determined by the rate of color disappearance at 504 nm of each well in a microplate reader (Spectramax Plus; Molecular Devices, Sunnyvale, CA). The UIC was determined by subtracting the OD of the blanks, and is expressed as µg/l against a standard iodine concentration (50-300 µg/l). The adequate values according to the UNICEF/WHO/ICCID (1) criteria were: exces-

sive UIC, > 250 µg/l; optimal iodine concentration, 150-200 µg/L; mild deficiency, 50-99 µg/l; moderate deficiency, 20-49 µg/l; and severe deficiency, < 20 µg/l. Serum TSH was measured using the Monobind Thryotropin Test System kit, and serum free T4 was measured with kit; both determinations were done with IMMULITE® 1000. The normal range of TSH and fT4 were considered as 0.39-6.16 UiO/ ml and 0.8-2.0 ng/dl, respectively.

ANTIOXIDANT STATUS

Catalase enzymatic activity was measured colorimetrically by the method of Sinha (27). The activity of SOD in erythrocytes was determined by the method described by Madesh and Balasubramanian (28). The total antioxidant status (TAS) was measured colorimetrically as reported (5), and hemoglobin, by the method previously described (29).

DETERMINATION OF OXIDATIVE STRESS BY TBARS

TBARS were measured in 90 µl of sample, which was mixed with 70 µl of TRIS (150 mM pH 7.5), 300 µl of mix with 0.4% of tiobarbituric acid, 20% acetic acid pH 3.0, and then, 90 µl of each sample were added. All samples were warmed to 100 °C during 45 minutes in a thermoblot. The samples were cooled in ice, and 1.2% of KCl was added. After centrifugation, 180 µl of overnadant were read and measured at 532 nm in a microplate reader (Spectramax Plus; Molecular Devices, Sunnyvale, CA). The results were expressed in absorbance units per 0.1 ml of sample nanomoles/gram hemoglobin.

STATISTICAL ANALYSIS

Data obtained were analyzed statistically using SPSS 17 for Windows (SPSS Inc., Chicago, IL, USA). The Student's t test and the ANOVA test were used to compare the continuous variables with normal distribution in two or more independent groups, whereas the Mann-Whitney U and Kruskal Wallis test were used for continuous variables with non-Gaussian distribution. Normally distributed data (CAT, FRP, TBARS, fT4 and creatinine) were expressed as means ± SD; non-normally distributed variables (SOD, THS and UIC) were expressed as medians (interval 5-95%). Differences with $p < 0.05$ were considered as significant. Spearman correlation tests were done with SPSS, and $p < 0.05$ were considered as significant.

RESULTS

A total of 57 eligible women consented to participate in the study. Table I presents data concerning sociodemographic and lifestyle variables. Mean age was 24.35 years (SD = 5.83; range = 15-40); 13.5% of controls and 20% of pregnant women had a history of preeclampsia and arterial hypertension. Maternal median UIC in the spot urine sample was 155.85 µg/l, with a range of 54.85-332.84 µg/l, and when was corrected for median urinary creatinine (168.9 µg/g creatinine). Seventy per cent (n = 14) of pregnant women with HPD had UIC between 50-149 µg/l, while 30% (n = 6) had the adequate level of 150-249 µg/l. As for control normotensive pregnant women, 24.32% (n = 9) had 50-149 µg/l, 48.64% had 150-249 µg/l (n = 18), and 27.02% (n = 10) had > 250 µg/l. Median values of the serum TSH in normotensive and HPD women were 1.7 ± 1.11 mIU/l, and 1.86 ± 1.58 mIU/l, respectively. While free T4 were 1.16 ± 0.17 ng/dl, and 1.07 ± 0.18 ng/dl, for normotensive and HPD women, respectively. The sub-clinical hypothyroidism (SCH), defined as elevated serum TSH with normal fT4 level, was seen among 14% (n = 8) of pregnant women, and none of them were found to be overt hypothyroid, although five pregnant women had iodine deficiency (50-149 µg/l) and four had HPD.

Table I. Sociodemographic characteristics from pregnant normotensive and HPD women

Characteristics	Cases (n = 20)	Control (n = 37)
Years (mean ± SD)	24.5 ± 6.06	24.21 ± 5.61
Education (years) (mean ± SD)	10.20 ± 2.04	10.22 ± 2.72
History of gestational hypertension and preeclampsia (%)	20	13.5
History of abortion (%)	20	10.8
History of stillbirth (%)	0	0
Primiparous (%)	50	54.1

The values of TBARS (oxidative stress), FRP, SOD, CAT activity (antioxidant status), TSH, fT4 and UIC are included in table II. We compared values between the normotensive and HPD groups, and significant higher levels of TBARS were found in the HPD group, 10.68 ± 2.9 *vs* 4.82 ± 1.13 µmol/l in normotensive pregnant women. Also, significant lower levels of SOD (2.29 ± 0.54 units mg/Hb), CAT (46.16 ± 8.8 units mg/Hb) and FRP (451.2 ± 29.2 µmol Fe2/l) enzymatic activities were found in the HPD group, compared to upper levels of SOD (3.5 ± 0.26 units mg/Hb), CAT (55.5 ± 9.53 units mg/Hb) and FRP (538.4 ± 29.3 µmol Fe2/l) in the normotensive pregnant control group. Likewise, significant lower levels of UIC were found in HPD (142.15 ± 84.8 µg/l) *vs* (185.7 ± 77.16 µg/l) in normotensive pregnant women ($p = 0.0174$). In table III, groups were separated in normotensive and HPD pregnant women with sufficiency, deficiency iodine levels, and differences in the biochemical parameters compared by the two-way ANOVA test. We found a significant statistical difference between UIC from HPD women with iodine deficiency *vs* HPD women with iodine deficiency ($p < 0.001$). In SOD activity low levels were found in HPD women vs normotensive pregnant women ($p < 0.05$). In normotensive pregnant women with sufficiency

Table II. Biochemical and hormonal parameters in normotensive and HPD pregnant women

Parameters	media ± DE	Median	Range	95% IC	p value
SOD (units mg/Hb)[a]					
Normotensive	3.6 ± 0.26	3.6	3.07-4.00	3.4-3.6	= 0.001*
HPD	2.29 ± 0.54	2.4	1.1-2.83	2.03-2.55	
CAT (units mg/Hb)					
Normotensive	55.5 ± 9.53	55.83	19.33-81.23	53.3-59.85	= 0.0317**
HPD	46.16 ± 8.8	46.83	37.36-57.03	40.04-48.28	
FRP (µmol Fe2/l)					
Normotensive	538.4 ± 29.3	537.3	485.83-603.61	528.5-548.4	= 0.001**
HPD	451.2 ± 29.2	460.8	401.56-488.40	437.6-464.9	
TBARS (µmol/l)					
Normotensive	4.82 ± 1.13	4.9	3.20-7.52	4.4-5.2	= 0.001**
HPD	10.68 ± 2.9	10.60	4.97-14.63	9.32-12.04	
TSH (µmlU/ml)[a]					
Normotensive	1.7 ± 1.11	1.3	0.31-5.66	1.3-2.0	= 0.9115
HPD	1.86 ± 1.58	1.37	0.51-6.07	1.1-2.6	
T4L (ng/dl)					
Normotensive	1.16 ± 0.17	1.18	0.83-1.60	1.10-1.22	= 0.0905
HPD	1.07 ± 0.18	1.03	0.69-1.29	0.98-1.15	
UIC (µg/l)[a]					
Normotensive	185.7 ± 77.16	176.4	54.39-291.97	159.6-211.8	= 0.0175*
HPD	142.15 ± 84.8	98.8	57.72-332.85	102-181	

*[a]There was not normal (Gaussian) distribution of the values, and the assessment was done on the basis of the median value. *Significance between normotensive and HPD women, Mann-Whitney test. **Significance between normotensive and HPD women-independent samples t test (paired t test).*

Table III. Biochemical parameters in normotensive and HPD pregnant women with sufficiency and deficiency iodine levels

Pregnant women	No.	SOD (units mg/Hb)	CAT (units mg/Hb)	FRP (µmol Fe2/l)	TBARS (µmol/)	TSH (µIU/ml)	hT4L (ng/dl)
Normotensive							
Iodine defficiency (< 149 µg/l)	11	3.5 ± 0.2[a]	59.8 ± 7.9[a]	532.9 ± 20.7[b]	4.8 ± 0.9[b]	1.4 ± 0.6	1.12 ± 0.1
Iodine sufficiency (> 150 µg/l)	25	3.6 ± 0.2[b]	55.1 ± 10.1[b]	540.9 ± 32.5[c]	4.8 ± 1.2[c]	1.8 ± 1.2	1.18 ± 0.1
Total	36	3.6 ± 0.2	55.1 ± 10.1	540.9 ± 32.5	4.8 ± 1.2	1.8 ± 1.2	1.18 ± 0.1
HPD							
Iodine deficiency (< 149 µg/l)	16	2.1 ± 0.5	43.3 ± 9.2	450.5 ± 30.7	10.3 ± 2.9	1.6 ± 1.3	1.0 ± 0.1
Iodine sufficiency (> 150 µg/l)	4	2.6 ± 0.2	47.4 ± 6.3	454.0 ± 26.0	11.8 ± 2.7	2.9 ± 2.1	0.9 ± 0.1
Total	20	2.6 ± 0.2	47.4 ± 6.3	454.0 ± 26.0	11.8 ± 2.7	2.9 ± 2.1	1.0 ± 0.1

Significant differences between media ± DE of normotensive and hypertensive pregnant women with two-way ANOVA test. [a]$p < 0.05$ between media ± DE of normotensive women with iodine deficiency vs HPD women with iodine deficiency. [b]$p < 0.001$ between media ± DE of normotensive women with iodine sufficiency vs HPD women with iodine sufficiency. [c]$p < 0.001$ between media ± DE of normotensive women with iodine deficiency vs HPD women with iodine deficiency.

and deficiency iodine levels, FRP (antioxidant status) was higher in comparison with HPD pregnant women ($p < 0.001$). Higher TBARS levels were found in HPD women with iodine sufficiency and deficiency compared with normotensive pregnant women ($p < 0.05$).

Table IV shows a significant positive correlation between normal UIC with SOD activity increase ($r = 0.354$, $p = 0.011$), although low UIC negatively correlated with HPD ($r = -0.281$, $p = 0.039$), suggesting that iodine deficiency and HPD are associated. In addi-

Table IV. Correlation between biochemical and hormonal parameters with iodine levels in normotensive and HPD pregnant women

Pregnant women	UIC		SOD		CAT		FRP		TBARS		TSH		T4L	
Normotensive	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**	**R**	**P**
Iodine defficiency	0.193	0.343	-0.508	0.110	-0.266	0.429	0.451	0.164	-0.221	0.514	-0.302	0.366	0.066	0.847
Iodine sufficiency	-0.062	0.638	0.398	0.011	0.080	0.768	-0.214	0.426	-0.111	0.683	0.078	0.774	0.273	0.306
HPD														
Iodine deficiency	-0.281	0.038	-0.975	0.025	-0.409	0.030	0.641	0.059	-0.562	0.078	-0.196	0.468	0.255	0.341
Iodine sufficiency	-0.362	0.113	-0.016	0.953	0.771	0.229	0.018	0.946	0.047	0.863	0.168	0.332	-0.340	0.660

tion, SOD ($r = 0.975$, $p = 0.025$) and CAT ($r = -0.409$, $p = 0.027$) activities correlate with HPD women with iodine deficiency.

DISCUSSION

This study shows that iodine deficiency is associated with hypertensive disease of pregnancy, as 70% of women with hypertensive disease of pregnancy had iodine deficiency with a median iodine level of 99.9 µg/l, as compared with 24.32% of normotensive women who had iodine deficiency with a median of 138.9 µg/l urinary iodine. This is consistent with previous studies that report a 45 mg/l UIC in pregnant women with preeclampsia (15,17). This data confirming that iodine deficiency is associated with hypertensive disease. In Mexico, the lack of nutritional information, as well as water contamination with heavy metals and consumption of foods rich in goitrous substances or junk foods, may be contributing to iodine deficiency in vulnerable groups such as children and pregnant women (30-32). However, further studies are required to determine the source of iodine deficiency in vulnerable groups, pregnant women and children specifically.

Oxidative stress is characterized by the presence of an excess of reactive oxygen species, outstripping the available capacity of antioxidants. This increase has been associated with various diseases such as cancer, atherosclerosis and preeclampsia (PE), among others (33-35). Imbalance between antioxidant defenses and lipid peroxidation leads to endothelial dysfunction and cell damage mediated by free radicals, altering trophoblast differentiation processes and migration to the uterine spiral arteries, and causing poor placentation and, consequently, pregnancy hypertensive disease (5,36,37). In pregnant women with preeclampsia, high levels of oxidative stress and low antioxidant status were found (38). It has been suggested to free radicals, superoxide anions primarily as promoters of maternal vascular malfunction, causing endothelial dysfunction (11), which leads to PE. About this study in pregnant women with hypertensive disease of pregnancy, they showed high levels of oxidative stress and low levels of antioxidant enzymes such as SOD, CAT and total antioxidant status compared with normotensive pregnant women. In this regard, our results clearly show high levels of markers of oxidative stress in pregnant women with HPD and low antioxidant levels, as reported by other authors (39-41); however, they are accented in pregnant women with iodine deficiency.

Micronutrient deficiency has been associated with increased oxidative stress during pregnancy. In this regard, this study shows for the first time that pregnant women with normal levels of iodine have significantly increased activity of SOD enzyme, compared with pregnant women with HPD, where it is decreased, indicating that normal iodine levels contribute to redox balance during pregnancy. In this respect, previous studies with iodine deficient rats showed that supplementation with potassium iodide increases the antioxidant activity in retina, an effect that is mediated by an increase of glutathione peroxidase (42). Similarly, patients with type II diabetes mellitus who received iodine brine drinking cure had increased antioxidant levels due to increased GSH-Px activity (43), indicating an antioxidant effect of iodine. In this study, pregnant women with HPD had low levels of SOD and CAT enzymes, decreased total antioxidant status and increased oxidative stress compared to normotensive pregnant women. On the other hand, normotensive pregnant women with normal levels of iodine had high levels of SOD and CAT enzymes and antioxidant status, as well as low oxidative stress compared to pregnant women with HPD, indicating that adequate levels of iodine contribute to redox maintenance during pregnancy. In addition, it has been shown that iodine deficiency alters trophoblast differentiation and induced an aberrant migration mediated by ROS increase, suggesting that iodine deficiency contributes to a dysfunctional endothelium and thus pregnancy complications (22). Besides iodine deficiency, other trace elements such as magnesium, selenium, copper, and iron were associated with PE (12). In conclusion, pregnant women with HPD had higher levels of oxidative stress and low antioxidant status, values accentuated in pregnant women with iodine deficiency, indicating that normal levels of iodine during pregnancy contribute to maintaining redox balance. In addition, these facts confirm that iodine deficiency is associated with HPD.

It is important to develop nutritional education programs aimed at women of reproductive age and pregnant women from the first trimester in order to avoid complications of pregnancy associated with micronutrient deficiency.

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